Chapter 8

Enhancing Genetic Testing for Rare Diseases: Improving Availability, Access, and Quality

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Genetic Testing for Rare Diseases

Although rare diseases and disorders are uncommon individually, they collectively affect a significant portion of the population. The majority of the 6,000–7,000 health conditions that at present are generally considered rare diseases are recognized as genetic conditions (1), making genetic testing an essential element in disease diagnosis and management. Rare diseases represent a major frontier in the development of genetic tests. Information from GeneTests (*www.genetests.org*), a publicly-funded information resource on genetic testing and its use in clinical practice, indicates that during a recent 10-month period, from May 2004 through March 2005, new genetic tests were introduced into clinical settings for more than 100 diseases, of which the majority were rare (2). Moreover, most newborn conditions found through screening are rare genetic diseases. With the current expansion of newborn screening programs, availability of and access to quality diagnostic genetic testing following screening has become a growing public health issue. *For more information on this topic, see Chapter 7, Newborn Screening for Cystic Fibrosis: A Public Health Response.*

Currently, the use of genetic testing is limited to only a small number of approved clinical laboratories and is available for only a small percentage of rare diseases. For many rare conditions, genetic testing may be available at only one or two laboratories in the United States, or even possibly worldwide, or at laboratories that primarily conduct research studies. As of March 2005, the GeneTests website (*www.genetests.org*) reported that clinical testing was available for 801 diseases, whereas testing for another 315 diseases was available only in research settings (2). Although GeneTests emphasizes information on DNA-based genetic tests, a huge gap exists in the availability of quality genetic testing—including molecular, biochemical, and other genetic tests—for rare diseases.

Genetic research is progressing rapidly, with an average of 60–100 new gene findings added each month to the Online Mendelian Inheritance in Man (OMIM) database (3). The total number of rare diseases is increasing as well, with approximately 20 additional rare diseases reported monthly in the scientific

literature (4). A limited survey of GeneTests conducted from August 2003 to April 2004, however, revealed that fewer than 10 new genetic tests per month had been added to the database (5), indicating a growing gap between our understanding of the genetic basis of diseases and the availability of quality clinical laboratory testing. This disparity is further aggravated, by the current lack of an established process to move potential tests for rare diseases from the research phase to a clinical laboratory setting. *For more information on this topic, see Chapter 6, Evaluation of Genomic Applications in Practice and Prevention: Implementation and Evaluation of a Model Approach.*

What Is a Rare Disease?

There is no uniform definition of a rare disease, although most definitions overlap. This report is not restricted to one single definition. Some examples of applicable definitions and their sources are as follows:

- A "rare disease or condition'' means any disease or condition which affects less than 200,000 persons in the United States. — The Orphan Drug Act (6).
- A rare or "orphan" disease affects fewer than 200,000 people in the United States. — National Organization of Rare Disorders (NORD) website (7).
- A rare disease (also called an orphan disease) is a disease or condition affecting fewer than 200,000 persons in the United States. An estimated 25 million people in the United States have a rare disease. — Office of Rare Diseases, National Institutes of Health (1).
- Diseases or conditions that affect or are manifested in fewer than 4,000 individuals in the United States per year.— 21 CFR 814 Premarket Approval Of Medical Devices; Subpart H: Humanitarian Use Devices (8).
- In Europe, a disease is considered as rare when it affects 1 person per 2,000 — Orphanet (4).

For many genetic conditions, the actual number of people with the condition is not well documented and prevalence must be estimated. Genetic researchers generally agree that most single-gene genetic conditions should be considered rare diseases, which currently comprise an estimated 6,000–7,000 diseases that together affect 25 million, or approximately 1 in 12 people in the United States.

Public Health Implications of Improving the Translation of Rare Disease Genetic Testing

In 2004, the Centers for Disease Control and Prevention (CDC) and other interested groups began to discuss how to improve the availability and quality of diagnostic rare disease testing and how public health could move the process forward. The goals were to:

- Assure access to quality laboratory testing.
- Promote translation of research into practice.
- Facilitate test development, validation, and implementation.
- Identify opportunities and barriers.
- Enhance information collection and synthesis.
- Promote collaboration, cooperation, partnership, and community involvement.

Promoting Quality Laboratory Testing for Rare Diseases: Keys to Ensuring Quality Genetic Testing

In May 2004, the conference "Promoting Quality Laboratory Testing for Rare Diseases: Keys to Ensuring Quality Genetic Testing" (9) was held in Atlanta, Georgia, as a collaborative effort of CDC, Emory University School of Medicine, the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH), the American Society for Human Genetics (ASHG), the American College of Medical Genetics (ACMG), the Health Resources and Services Administration (HRSA), and the Genetic Alliance. Conference participants included more than 50 experts from government, academic institutions, professional organizations, laboratories, industry, health care payers, and patient advocacy groups. The main goals of the conference included:

- Review of the current rare disease testing landscape.
- Discussion of the problems and concerns regarding the quality, availability, access, and resources for rare disease testing.
- Identification of needs and barriers to quality testing.
- Exploration of potential approaches to promoting quality testing.

- Development of specific recommendations and action items for improving availability of and access to quality laboratory testing for rare diseases.

The conference included plenary presentations on:

- Analyses of currently available genetic testing for rare diseases and recent trends.
- **CLIA** oversight of clinical laboratories.
- Roles of federal and institutional bodies in assuring safety and protection of human research subjects.
- Implications of the HIPAA Privacy Rule (10) for clinical research.
- Current working approaches that provide quality rare disease testing.
- Current strategies that facilitate translation of potential tests into practice.
- Past and current efforts to improve quality, availability, and access for rare disease genetic testing.

CLIA (Clinical Laboratory Improvement Amendments)
CLIA, 42 CFR Part 493, sets forth federal standards for laboratories performing patient testing to ensure the quality of laboratory testing in the United States.

Public Health Actions: Improving the Translation of Tests for Rare Diseases from Research to Clinical Practice

All attendees agreed upon the following goals and actions by the conclusion of the meeting:

- Provide education to promote quality translation of research findings into clinical testing for rare diseases and to advance understanding of quality standards for patient testing. Appropriate strategies and teaching materials should be developed for the research community, institutional review boards (IRBs), providers and users of laboratory services, health care payers, patients, research participants, and advocacy groups in order to minimize adverse impact on access to testing.
- Develop guidance, strategies, and criteria for evaluating the clinical readiness of potential tests. Issues needing further exploration include how recently developed rare disease tests should be validated and how analytic validity, clinical validity, and clinical utility should be established for these tests. *For more information on this topic, see Chapter 5, ACCE Reviews of Genetic Tests: BRCA1, BRCA2 and CFTR.*

- Develop reasonable and achievable **quality assurance** strategies for clinical genetic testing for rare diseases.

- Establish mechanisms and strategies to promote quality data collection during each step of test development through clinical application.

- Establish partnerships and networks to improve and facilitate research translation, data sharing, clinical availability, and quality assurance.

- Enhance infrastructure to provide momentum and enable development of activities needed, including facilitating the translation process, assuring the quality of testing services, and improving access to testing.

Quality assurance (QA)
QA includes all actions taken to ensure that laboratory standards and protocols are adhered to, and that test results consistently meet performance requirements.

Public Health Actions: Ensuring Access and Quality of Rare Disease Testing

The conference concluded with the following immediate outcomes and next steps:

- Agreement was made to form the North American National Laboratory Network for Rare Disease Genetic Testing with six reference laboratories (11).

- The American Society of Human Genetics and other professional organizations agreed to organize educational activities and develop guidance for rare disease genetic testing.

- The Office for Human Research Protections (OHRP) confirmed its commitment to providing education to IRBs regarding their role in safeguarding the release of individual test results in clinical research (12).

- Agreement was made to hold a follow-up "Integration Conference" in 2005 to convert the recommendations into projects and action items and to develop additional recommendations.

To accomplish these goals, public health professionals will need to develop an infrastructure for guiding the process that would include strategies for determining how best to translate rare disease tests from research to clinical testing; how to ensure that access is not lost as the quality of testing is emphasized; and how to decide which tests public health efforts should focus on first.

References

1. Office of Rare Diseases, National Institute of Health [website] [cited 2005 Mar 25]. Available from URL: *http://rarediseases.info.nih.gov*.

2. GeneTests: Medical Genetics Information Resource [database online]. University of Washington, Seattle. 1993-2005. Updated weekly. [cited 2005 March 25]. Available from URL: *http://www.genetests.org*.

3. Online Mendelian Inheritance in Man (OMIM). [online].[cited 2005 Mar 25]. Available from URL: *http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM*.

4. Orphanet [website] [cited 2005 Mar 25]. Available from URL: *http://orphanet.infobiogen.fr/*.

5. Promoting Quality Laboratory Testing for Rare Diseases: Keys to Ensuring Quality Genetic Testing Conference, 2004 May 20-21, Atlanta, GA. General Session I. Genetic Testing for Rare Diseases, Oversight Issues, and Public Needs. [online] [cited 2005 Mar 25]. Available from URL: *http://www.phppo.cdc.gov/dls/genetics/RareDisease/GeneralSessions.aspx*.

6. The Orphan Drug Act. [online]. [cited 2005 Mar 25]. Available from URL: *http://www.fda.gov/orphan/oda.htm*.

7. National Organization of Rare Disorders. [online] [cited 2005 Mar 25]. Available from URL: *http://www.rarediseases.org*.

8. 21 CFR 814 Premarket Approval of Medical Devices; Subpart H: Humanitarian Use Devices. [online] [cited 2005 Mar 25]. Available from URL: *http://www.fda.gov/orphan/HUDS/cfr814.html*.

9. Promoting Quality Laboratory Testing for Rare Diseases: Keys to Ensuring Quality Genetic Testing conference, May 20-21, 2004, Atlanta, GA. [online] [cited 2005 Mar 7]. Available from URL: *http://www.phppo.cdc.gov/dls/genetics/RareDiseaseConf.aspx*.

10. Summary of the HIPAA Privacy Rule [PDF online] [cited 2005 Mar 7]. Available from URL: *http://www.hhs.gov/ocr/hipaa/*.

11. National Laboratory Network for Rare Disease Genetic Testing [online]. [cited 2005 Mar 25]. Available from URL: *http://www.rarediseasetesting.org*.

12. Office for Human Research Protections. [online] [cited 2005 Mar 25]. Available from URL: *http://www.hhs.gov/ohrp/*.